Office Action Summary	Application No.	Applicant(s)	
	10/827,023	BLAZAR ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-11 and 28-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-11 and 28-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Q. Janice Li, at Group Art Unit 1633.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/21/08 has been entered.

The amendment and remarks submitted 4/21/08 are acknowledged. Claims 1-5, 7-11, 28, 29 have been amended, claims 30-35 are newly added. Claims 1-5, 7-11, 28-35 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and new grounds of rejections will not be reiterated.

Claim Objections

Claim 1 is objected to because of the unspecified acronym "GMP". Appropriate correction is required.

Claim 3 is objected to because the word "said" in line 1 should not have been deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7-11, 28-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are rejected because claim 1 recites "GMP-approved methods". The specification and the claims fail to teach what the methods are, and thus, the meets and bounds of the claims are unclear.

Claims 2 and 32 are vague and indefinite because it is unclear what positive step is encompassed by an isolation step "comprises a high level of stringency", and thus the metes and bounds of the claims are uncertain. Further, the specification does not provide a standard for ascertaining the requisite degree of the recited high stringency, and one of the skill in the art would not be reasonably apprised of the scope of the invention.

Claim 3 is vague and indefinite because of the claim recitation "wherein isolation step further comprises substantially enhancing CD4+CD25^{bright} cells in

said isolated population, while substantially depleting $CD25^{dim}$ cells in said isolated population". It is unclear what steps and means the claim encompasses, and hence the metes and bounds of the claims are uncertain.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-11, 28-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for providing human T regulatory (Treg) cells with *enhanced suppressor activity* under the conditions now claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction

or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are directed to a method for producing therapeutic human T regulatory cells with enhanced suppressor activity, wherein a critical step as now claimed is culture-expanding the CD4+CD25+ Treg cells with immobilized anti-CD3/CD28 at the ratio of less than one. The specification contemplates providing Treg cells with enhanced suppressor activity. The specification briefly mentions when various ratios of anti-CD3 to anti-CD28 were tested on the microbeads, the higher ratio anti-CD28 beads induced selective outgrowth of suppressor T cells (Specification, paragraph bridging pages 25-26). From this teaching, it appears the suppressor activity of Treg cells are simply regulated by proper ratios of of anti-CD3 to anti-CD28.

Turning to the state of the art, it recognizes the complex regulatory factors determine the suppressor function of Treg cells. *Chen* (Cytokine Growth Factor Rev 2003;14:85-89) teaches, "FOLLOWING THE ORIGINAL IDENTIFICATION OF A SMALL, BUT POWERFUL, POPULATION OF $CD4^{+}CD25^{+}$ T CELLS WHICH CAN DRAMATICALLY SUPPRESS IMMUNE RESPONSIVENESS. THERE HAS BEEN AN ENORMOUS EFFORT TO DISSECT THE MECHANISMS BY WHICH THESE CELLS EXERT THEIR SUPPRESSIVE PROWESS. IN A SHORT PERIOD OF TIME, $CD4^{\pm}CD25^{\pm}$ REGULATORY T CELLS HAVE GENERATED SO MUCH INTEREST IN IMMUNOLOGY BECAUSE OF THEIR RECOGNIZED IMPORTANCE IN TOLERANCE, AUTOIMMUNE DISEASES, TRANSPLANTATION, CANCER AND INFECTIOUS DISEASES. NONETHELESS, THE MECHANISMS UNDERLYING THEIR ABILITY TO SUPPRESS IMMUNITY REMAIN ILL DEFINED AND HOTLY CONTESTED" (Introduction, emphasis added). At the time, *Chen* acknowledges that suppressor T cell function is a complex process, tightly

regulated by multiple factors, including IL-2, CTLA-4, and glucocorticoid induced TNF receptor. Hence, although anti-CD3/anti-28 ratio may participate in the regulatory process, given the state of the art, a brief statement regarding anti-CD3/anti-28 ratio as the define element and the sole support of instant claims is unlikely to be sufficient.

This conclusion is supported by another publication in the art. *Baecher-Allan* (J Immunol 2001; 167:1245-530) reports the anti-CD3/CD28 ratio and the suppressor function of the CD4+CD25+ cell population. As shown in figure 3, the conditions tested including different concentrations of anti-CD3, and the presence or absence of anti-CD28 (at a constant concentration 5mg/ml). The anti-CD3/CD28 ratio from left to right panel of figure 3 is 1:1, 1:10, and 2:1, respectively. As an initial matter, it is noted within each panel, the Treg cells asserts greater suppressor function in the presence of anti-CD3 alone without anti-CD28. This observation contradicts the applicant's conclusion that higher amount of anti-CD28 would enhance suppressor function of Treg cells. It is also noted although there was higher suppressor activity when the ratio was 1;10 compared to 1:1, there was no significant difference of the suppressor activity between the ratio 1:10 and 2:1. At ratio 1:1, the suppressor function was significantly diminished compared to the absence of anti-CD28, or compared to ratio 2:1. This observation would lead to the conclusion that the suppressor activity of Treg cells is not determined by the anti-CD3/CD28 ratio alone in the context of culturing human CD4+CD25+ Treg cells. Moreover, it is noted that IL-2 may enhances the proliferation of Treg cells but not the suppressor activity of

Treg cells. In view of such, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the references. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

Furthermore, it appears, in the specification, all of the experimental data were obtained by expanding Treg cells at the anti-CD3/CD28 ratio at 1:1 because the specification cited *Levine et al* for experimental protocol, who uses the anti-CD3/CD28 ratio at 1:1, and the specification uses the commercially available Dynabeads CD3/CD28 expander (Specification, paragraph 0026 and example 8), which was coated at ratio 1:1 (see Dynabeads datasheet). Accordingly, the specification fails to provide sufficient evidence to contradict what was known in the art at the time, and fails to support what is now claimed.

Claims 4 and 34 are directed to enhancing CD4+CD25^{bright} cells in the isolated CD4+CD25+ cell population by using less volume of beads compared to manufacture recommended volume (2 μl vs. 10 to 20 μl). However, it appears the criteria was derived from the cell sorting *Baecher-Allan* teaches that CD25 bright (high) or dim (low) reflects the strength of TCR signal (e.g. figures 1-2), and hence contacting the CD25 bright cells with less beads would lead to incomplete collection of CD4+CD25^{bright} cells, but not necessarily enhance the CD4+CD25^{bright} cells in the isolated CD4+CD25+ cell population. The specification fails to teach using the 2ml volume beads would enhance CD4+CD25^{bright} cells compared to the manufacture recommended volume, and thus fails to provide an enabling disclosure for what is now claimed.

Therefore, in view of the limited guidance, the knowledge of the skilled in the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7-11, 28-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Schuler et al*. (US 2005/0101012 A1), in view of *Baecher-Allan et al.* (J Immunol 2001; 167:1245-530, IDS) and CD25 Microbeads Datasheet (Miltenyi, publicly available at least on Nov. 1996 as evidenced by *Elkord*, Biocompare Review, 1996).

Schuler teaches a method for generating human T regulatory cells, the method comprises contacting a sample of human CD4+ T cells with anti-CD25 antibody to produce an isolated population of human CD4+CD25+ Treg cells

(see e.g. fig. 1A); *Schuler* also teaches expanding CD4+CD25+ Treg cells *ex vivo* in the presence of stimulation agents, wherein anti-CD3 and anti-CD28 antibodies are on top of the list (e.g. paragraph 0035-0036). *Schuler* teaches, similar to their murine counterparts, the human CD4+CD25+ T cells showed almost no proliferation upon polyclonal activation by plate-bound anti-CD3/anti CD28, but when combined with IL-2, the proliferation was significantly enhanced (col 2, page 4, and fig 2). Fig. 2D shows increased production of CD4+CD25+ Treg cells in the presence of IL-2, IL-15. *Schuler* teach the positive selection through MACS-sorted process provides a more than 95% pure population of CD4+CD25+ cells (Specification, paragraph 0081), and thus the isolation step meets a high level stringency standard.

Although *Schuler* uses immobilized anti-CD3 and soluble anti-CD28, apparently the plate-bound anti-CD3/CD28 was known in the art as mentioned by *Schuler*, and appears to fall within the bounds of experimental preference and optimization, the two means do not appear to be patentably distinct.

The claims are directed to adjusting cell numbers:beads volume ratio to enhancing CD4+CD25^{bright} cells in the isolated cell population and multiple rounds of magnetic column separation and elution. Although *Schuler* in view of *Baecher-Allan* do not teach these technical details, these were knowledge known in the art as disclosed in the CD25 MicroBeads Datasheet, wherein the manufacture teaches adjusting cell/beads ratio for different purpose (e.g. the table in § 2.2), and multiple rounds of column separation and elution (see the protocol in § 2.3.

As to the direct and indirect antibody conjugation, the technique was well established in the art. While the CD25 may well be directly conjugated to the beads through magnetic sorting process as used by *Schuler*, *Schuler* as well as *Baecher-Allan* (column 2, page 1246) also teaches toxin-, FITC- or PE-conjugated antibodies (Specification, paragraph 0045, 0048). Accordingly, these limitations fall within bounds of experimental preference and optimization.

Schuler differs from instantly claimed method in that they used the anti-CD3 and anti-CD28 at a ratio that equals to one, not less than one; and *Schuler* did not distinguish CD25 bright or dim population.

Baecher-Allan supplemented the deficiency by establishing it was known in the art that CD25 population could further divided into bright (high) and dim (low), and *Baecher-Allan* use the CD+CD25^{high} population for the suppressor functional test (e.g. figures 1-3). *Baecher-Allan* supplemented the deficiency by establishing it was also well known in the art when the antibodies were at a ratio 1:10 (less than 1:5), the suppressor function is significantly higher compared to ratio 1:1 (figure 2, bottom row).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Schuler* with that of *Baecher-Allan* by using anti-CD3 and anti-CD28 at a ratio of less than one and following through the manufacture's protocol for isolating CD4+CD25+ cell population and adjusting the cell/beads ratio for different purpose with a reasonable expectation of success. As to the "long term" limitation, the specification defines it as longer culture duration, or "for a period at least 3-fold

longer than the control group". Although the combined teachings did not specify the folds of expansion or culture duration, since the combined teachings would have arrived at the same method steps as now claimed, the fold of expansion and the term of culture duration would have met the limitation as recited in the claims. Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7:30 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

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